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Near-roadway air pollution associated with COVID-19 severity and mortality – Multiethnic cohort study in Southern California

Zhanghua Chen [a,1], Brian Z. Huang [a,b,1], Margo A. Sidell [b,1], Ting Chow [b], Sandrah P. Eckel [a], Nathan Pavlovic [c], Mayra P. Martinez [b], Fred Lurmann [c], Duncan C. Thomas [a], Frank D. Gilliland [a], Anny H. Xiang [b,*]

[a] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States
[b] Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA, United States
[c] Sonoma Technology, Petaluma, CA, United States

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ABSTRACT

Background: Air pollution exposure has been associated with increased risk of COVID-19 incidence and mortality by ecological analyses. Few studies have investigated the specific effect of traffic-related air pollution on COVID-19 severity.

Objective: To investigate the associations of near-roadway air pollution (NRAP) exposure with COVID-19 severity and mortality using individual-level exposure and outcome data.

Methods: The retrospective cohort includes 75,010 individuals (mean age 42.5 years, 54% female, 66% Hispanic) diagnosed with COVID-19 at Kaiser Permanente Southern California between 3/1/2020–8/31/2020. NRAP exposures from both freeways and non-freeways during 1-year prior to the COVID-19 diagnosis date were estimated based on residential address history using the CALINE4 line source dispersion model. Primary outcomes include COVID-19 severity defined as COVID-19-related hospitalizations, intensive respiratory support (IRS), intensive care unit (ICU) admissions within 30 days, and mortality within 60 days after COVID-19 diagnosis. Covariates including socio-characteristics and comorbidities were adjusted for in the analysis.

Result: One standard deviation (SD) increase in 1-year-averaged non-freeway NRAP (0.5 ppb NO_x) was associated with increased odds of COVID-19-related IRS and ICU admission [OR (95% CI): 1.07 (1.01, 1.13) and 1.11 (1.04, 1.19) respectively] and increased risk of mortality (HR = 1.10, 95% CI = 1.03, 1.18). The associations of non-freeway NRAP with COVID-19 outcomes were largely independent of the effect of regional fine particulate matter and nitrogen dioxide exposures. These associations were generally consistent across age, sex, and race/ethnicity subgroups. The associations of freeway and total NRAP with COVID-19 severity and mortality were not statistically significant.

Conclusions: Data from this multiethnic cohort suggested that NRAP, particularly non-freeway exposure in Southern California, may be associated with increased risk of COVID-19 severity and mortality among COVID-19 infected patients. Future studies are needed to assess the impact of emerging COVID-19 variants and chemical components from freeway and non-freeway NRAP.

1. Introduction

Several national and international studies have linked long- and short-term air pollution exposure to the incidence and mortality of the Coronavirus Disease 2019 (COVID-19). (Wu et al., 2020; Bianconi et al., 2020; Liang et al., 2020; Ogen, 2020; Andrée, 2020; Yao et al., 2020; Travaglio et al., 2021; Pozzer et al., 2020; Hutter et al., 2020; Frontera et al., 2020) Air pollution exposure may increase the susceptibility of severe COVID-19 due to the adverse effect on comorbidities such as chronic respiratory and cardiometabolic diseases. (Langrish et al., 2012;

* Corresponding author at: Department of Research & Evaluation, Kaiser Permanente Southern California, 100 S Los Robles Ave, Pasadena, CA 91101, United States.

E-mail address: anny.h.xiang@kp.org (A.H. Xiang).

[1] Co-first authors.

An et al., 2018; Lawal, 2017; Lin et al., 2018; Chen et al., 2015; Chen et al., 2016) At the same time, short-term air pollution exposure may also increase the risk of COVID-19 severity through the air pollution-induced immunotoxicity and inflammation. (Calderón-Garcidueñas et al., 2009; Stanek et al., 2011) Most previous studies have focused on the associations with regional air pollutants exposures such as fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2), and findings were mostly drawn from ecological analyses using population-level data on air pollution exposure and COVID-19 outcomes aggregated over various geospatial areas. It is known that the ecological study design has limitations that can lead to biased results, such as potential mis-classifications of exposure and outcomes and uncontrolled confounders across heterogeneous populations. Therefore, there is a need for investigations at the individual level in multiethnic cohorts adjusting for key socio-demographic characteristics and comorbidity covariates. (Villeneuve and Goldberg, 2020)

Traffic emissions are main contributors to ambient air pollution, especially in urban cities. To our knowledge, only one ecological study has used land-use regression models to predict NO_2 exposure in 2016 as an estimate of long-term traffic-related air pollution exposure and assessed its association with COVID-19 incidence and mortality in Los Angeles. (Lipsitt et al., 2021) However, the effect of ambient air pollution exposure was not adjusted for and the interpretation of the results is limited by the population-level outcome and exposure data. The COVID-19 lockdown has also significantly reduced traffic volumes, (Parker et al., 2020) which was not studied in that analysis and would require better exposure assessment, specifically for near-roadway air pollution exposure (NRAP) mixture from different sources of freeways and non-freeways. To fill these gaps, we investigated the associations of COVID-19 severity and mortality with longer- and shorter-term NRAP exposure estimated by line-source dispersion models, which incorporate measures of traffic volume, vehicle emissions, and meteorological data to produce concentrations of NRAP separately from freeway and non-freeway sources. Our study was built upon a multiethnic cohort of COVID-19 patients from a large integrated health care system in Southern California with a well-established electronic medical records (EMR) system. NRAP exposure was estimated using individual residential address history, while severity and mortality outcomes after COVID-19 diagnosis and a spectrum of comorbidities and socioeconomic characteristics were extracted from the EMR.

2. Methods

2.1. Cohort

This is a retrospective cohort study with data collected from EMR at Kaiser Permanente Southern California (KPSC), a large integrated healthcare system with over 4.5 million members across Southern California. The number of KPSC members is around 20% of the entire population of Southern California. KPSC membership is diverse and similar in socioeconomic characteristics to the region's census demographics. (Koebnick et al., 2012) The cohort included individuals diagnosed with COVID-19 at KPSC between March 1, 2020 to August 31, 2020 (n = 82,213) with follow-up up to October 31, 2020. Positive COVID-19 diagnosis was defined as a positive SARS-CoV-2 polymerase chain reaction (PCR) lab test result or a diagnosis code (ICD-10 and internal KPSC codes) for COVID-19 (Supplemental Table 1). Individuals with a negative lab result within two weeks following an asymptomatic COVID-19 diagnosis code were excluded to avoid potential false positives. The index date was defined as the earliest lab order for those with lab data or the earliest COVID-19 diagnosis code for those with only diagnosis codes. Individuals under 12 years of age (n = 2409), non-KPSC health plan members with incomplete medical records (n = 1365), or individuals with incomplete address information for air pollution exposure assignment (n = 3423) or unknown gender (n = 6) were excluded. The final study cohort included 75,010 patients, of whom

61,689 (82.2%) had positive PCR lab results. This study was approved by the KPSC Institutional Review Board with waiver of informed consent.

2.2. Air pollutant exposures

NRAP exposure was estimated by the California Line Source Dispersion Model (CALINE4) through detailed residential history, where residential address history during one year prior to index date was extracted from a consolidated address history table from Geographically Enriched Member Sociodemographic (GEMS) DataMart created by the KPSC Utility for Care Data Analysis (UCDA). Residential addresses were geocoded using ArcGIS and geocode quality was assessed based on the three ArcGIS variables: STATUS (matched, tied, unmatched), SCORE (0–100), and ADDRESS TYPE (point address, street address, street name, postal). Because the traffic pollution assignments are sensitive to the geographic accuracy of the residence locations relative to major roads, only the highest quality addresses were included. The criteria were that the addresses were "matched," with a score of 98–100, and with "point address" or "street address" types, which indicates they are geo-referenced to a parcel or interpolated by address number between known cross streets. The CALINE4 model (Benson, 1989) then estimates NRAP using the concentrations of NO_x at each latitude and longitude for freeway and non-freeway roads using traffic emissions (California Air Resources Board, 2017) (calculated within a 5-km buffer of the residence), traffic volume, roadway geometry and meteorological conditions (NOAA, 2021) including wind speed and direction, pollution mixing heights, and atmospheric stability. Like other Gaussian dispersion models, such as AERMOD and RLINE, CALINE4 is a steady state model that estimates 1-hour average concentrations assuming the wind speed, wind direction, vehicle emissions, and atmospheric stability are locally constant each hour. The CALINE4 model has been evaluated against near-road hourly observations in numerous studies and has demonstrated reasonable performance for a variety of inert pollutants in different roadway and meteorlogical settings. (Levitin et al., 2005; Benson, 1992; Kenty et al., 2007; Yura et al., 2007) Several model intercomparison studies report similar performance of the RLINE, AERMOD, ADMS, and CALINE4 models. (Chen et al., 2009; Heist et al., 2013) The results from CALINE4 have also been used in numerous epidemiologic studies to assess associations of near-read air pollution and various health outcomes. (Farzan et al., 2021; Chen et al., 2019; Kim et al., 2018; Weaver and Gauderman, 2018)

It is noted that the CALINE4 estimates of NRAP quantified by NO_x is a surrogate for the mixture of gaseous and particle pollutants emitted from vehicles running on freeways and non-freeways. Traffic volumes, speeds, and heavy-duty truck volumes were obtained from Caltrans real-time Performance Measurement System (PeMS) for major roads and the Streetlytics™ data by Bentley Systems, Inc. (www.bentley.com) for all other roads. The daily PeMS traffic volumes from mid-March to mid-April show 38% lower total vehicle volumes and 25% lower truck volumes on major roads than in the first 2.5 months of 2020. The PeMS daily traffic data in 2019–2020 was used to account for the large reductions from "normal" traffic during the shelter-in-place period compared to other periods. The road geometry was based on the detailed and spatially accurate 2019 HERE Technologies roadway network data (https://www.here.com/). The CALINE4 model has been applied using the hourly meteorology and traffic volumes for individual days at each residence and then averaged to assign the freeway NRAP, non-freeway NRAP and total NRAP (sum of freeway and non-freeway NRAP) for the 1-month (shorter-term) and 1-year (longer-term) average traffic-related air pollution exposures prior to the COVID-19 diagnosis. The estimates incorporate residence changes during the exposure periods.

Shorter- and longer-term average exposures to regional air pollutants including $PM_{2.5}$ and NO_2 were estimated for residential addresses based on hourly and daily air quality data from ambient monitoring stations reported to the U.S. Environmental Protection Agency's Air Quality

System (U.S. Environmental Protection Agency's Air Quality System, 2021) and the California Air Resources Board's Air Quality and Meteorological Information System. The regional $PM_{2.5}$ and NO_2 were adjusted for in the exploratory analysis to assess the independent effect of NRAP.

2.3. COVID-19-related severity and mortality outcomes

The primary outcomes included COVID-19 severity defined as COVID-19-related hospitalizations, intensive respiratory support (IRS), and intensive care unit (ICU) admissions within 30 days after the index date, and mortality within 60 days. COVID-19-related hospitalization and ICU admissions were obtained from inpatient records and out-of-network claims with associated COVID-19 ICD codes. IRS was defined as having any use of invasive mechanical ventilation, non-invasive ventilation, high flow nasal cannula, or high flow mask with associated COVID-19 ICD codes. Mortality was obtained from EMR mortality and inpatient data.

2.4. Covariates

Demographics (age, sex, race/ethnicity), Medicaid insurance status, body mass index (BMI), smoking history, and history of other comorbidities at the time of COVID-19 diagnosis were obtained from the KPSC EMR. BMI categories were calculated based on CDC definitions of underweight/normal (<25 kg/m^2), overweight (25 to <30 kg/m^2), obese class 1 and 2 (30 to <40 kg/m^2), and obese class 3 (40 kg/m (Bianconi et al., 2020) or higher). The Charlson comorbidity index was calculated using diagnosis codes within 12-month prior to COVID-19 diagnosis and categorized to none, one, or at least two comorbidities. (Quan et al., 2005) Neighborhood-level education and income information were estimated using Nielsen demographic data. (Nielsen Demographic Data, 2021) Medical center was derived from utilization records within the prior year or the medical center where COVID-19 diagnosis was confirmed if prior utilization was unavailable.

2.5. Statistical analysis

Correlations among freeway, non-freeway and total NRAP as well as among regional $PM_{2.5}$ and NO_2 across shorter- and longer-term periods were assessed using Pearson correlation coefficients. We first used single pollutant models to assess the association of each NRAP exposure at each time window with each outcome. For severity outcomes, mixed effects logistic regression models were used to estimate the odds ratios (OR) associated with NRAP, with medical center included as a random effect to account for potential within-center correlations. For mortality within 60 days, survival models with medical center as a cluster variable with sandwich variance estimators were used to estimate and test for the significance of the hazard ratios (HR) associated with time to death within 60 days. Individuals were censored at 60 days after index date, date of death, end of membership, or end of study (October 31, 2020), whichever occurred first, to focus on deaths related to COVID-19 incidence.

All models were adjusted for age (<35, 35–64, ≥65 years), race/ethnicity (white, Black, Asian, Hispanic, other), sex, BMI (underweight/normal, overweight, obese (class 1 and 2), obese (class3), smoking status (current, former, never), Charlson comorbidity index (0, 1, ≥2), Medicaid insurance status, median neighborhood income ($<\$40,000$, $\$40,000–\$79,999$, $\geq\$80,000$), and college education (based on neighborhood proportion of highest education). To adjust for temporal variations of the COVID-19 pandemic, indicators for month of COVID-19 diagnosis were included. To investigate whether the associations of NRAP with COVID-19 outcomes were independent from regional air pollutants exposure, we ran separate models that additionally adjusted for regional NO_2 and $PM_{2.5}$ exposures. Potential effect modifications by age, sex, and race/ethnicity were assessed using multiplicative

interactions between these covariates and exposures. Sensitivity analysis were performed to assess the potential non-linear relationships of NRAP and age as a covariate with the four outcomes using generalized additive models with a cubic smoothing spline. All ORs and HRs along with 95% confidence intervals (CI) are scaled to a one standard deviation (SD) increase in exposure. Analyses were conducted using SAS version 9.4 (Cary, NC) or R version 3.6.0.

3. Results

Among the 75,010 total COVID-19 patients diagnosed from March to August 2020, the mean (SD) age was 42.5 (16.5) years; 53.7% were females; 65.8% were Hispanic; 76% were overweight or obese; 16.1% were former and 5.2% current smokers; and 28.8% had a history of comorbidity (Table 1). 4757 (6.3%) individuals had a COVID-19-related hospitalization, 1764 (2.4%) had COVID-19-related IRS, and 1125 (1.5%) had a COVID-19-related ICU admission within 30 days after COVID-19 diagnosis, while 1090 (1.5%) died within 60 days after COVID-19 diagnosis. Associations between key socio-characteristic variables and COVID-19 outcomes are presented in Supplemental Table 2.

Means (SDs) of estimated NO_x for 1-year averaged freeway, non-freeway and total NRAP were 1.0 (1.3), 0.7 (0.5) and 1.7 (1.5) ppb, respectively. Means (SDs) of 1-month averaged freeway, non-freeway and total NRAP were lower than 1-year averaged NRAP exposure and were 0.8 (1.1), 0.5 (0.4) and 1.3 (1.3) ppb, respectively (Table 1). There were strong temporal correlations between one-month and one-year averaged exposures (R $>$ 0.9 for freeway, non-freeway and total NRAP). Since the total NRAP is mostly attributable to the freeway NRAP, there was a high correlation between freeway and total NRAP for both 1-month and 1-year averaged exposures (R $>$ 0.85). However, non-freeway NRAP had low correlation with freeway NRAP (R $=$ 0.1) (Supplemental Table 3).

No statistically significant departure from linear relationships were observed between non-freeway NRAP and COVID-19 outcomes (p for cubic spline term $>$ 0.05). Both longer- and shorter-term non-freeway NRAP was associated with COVID-19 severity and mortality after adjusting for covariates (Fig. 1). However, no significant associations were observed between freeway NRAP or total NRAP with COVID-19 severity and mortality (Fig. 1). One-year averaged non-freeway NRAP was associated with increased risk of COVID-19-related IRS (odds ratio per 1 SD of 0.5 ppb in NO_x, OR $=$ 1.07, 95% confidence internal, CI $=$ 1.01, 1.13), ICU admission [OR (95% CI) $=$ 1.11 (1.04, 1.19)], and mortality (hazard ratio, HR $=$ 1.10, 95% CI $=$ 1.03, 1.18). One-month averaged non-freeway NRAP had similar associations with COVID-19-related ICU admission and mortality [OR (95% CI) per 1 SD of 0.4 ppb in $NO_x =$ 1.11 (1.04, 1.19) for ICU admission; HR (95% CI) $=$ 1.09 (1.01, 1.17) for mortality], but was not significantly associated with IRS [OR (95% CI) $=$ 1.05 (0.99,1,11)]. No significant associations were observed for either 1-year or 1-month averaged non-freeway NRAP with COVID-19-related hospitalization. Sensitivity analysis with adjustment for age as a cubic spline in the model showed that findings did not significantly differ from the adjustment using categorical age (Supplemental Table 4).

After additionally adjusting for regional $PM_{2.5}$ and NO_2 exposures, the associations of longer- and shorter-term non-freeway NRAP were attenuated by 19–26% (Fig. 2). However, the associations of 1-year averaged non-freeway NRAP with COVID-19-related ICU admission and mortality were still statistically significant [OR (95% CI) $=$ 1.08 (1.02, 1.16) for ICU admission and HR (95% CI) $=$ 1.08 (1.01, 1.16) for mortality]. One-month non-freeway NRAP was also associated with higher odds of COVID-19-related ICU admission after adjusting for regional $PM_{2.5}$ and NO_2 exposures [OR (95% CI) $=$ 1.08 (1.01, 1.16)]. However, the association between 1-month non-freeway NRAP and COVID-19-related mortality was attenuated by 21% and was not statistically significant after adjusting for regional air pollutants exposure [HR (95% CI) $=$ 1.07 (0.99, 1.15)].

Table 1

Characteristics of Study Cohort and Pollution Exposure Distribution among COVID-19 patients diagnosed from 3/1–8/31/2020 at Kaiser Permanente Southern California (N = 75,010).

	Total COVID-19 Cases (N = 75,010)
Age	
Mean (SD), y	42.5 (16.5)
By age group, N (%)	
<35 y	28,836 (38.4)
35–64 y	38,977 (52)
>= 65 y	7197 (9.6)
Gender, N (%)	
Female	40,290 (53.7)
Male	34,720 (46.3)
Race/ethnicity, N (%)	
Asian/Pacific Island	4798 (6.4)
Black	4384 (5.8)
Hispanic	49,380 (65.8)
Other	5038 (6.7)
White	11,410 (15.2)
BMI category, N (%)	
Underweight/Normal	14,129 (18.8)
Overweight	22,371 (29.8)
Obese (class 1 and 2)	27,705 (36.9)
Obese (class 3)	6990 (9.3)
Missing	3815 (5.1)
Tobacco use, N (%)	
Current	3937 (5.2)
Former	12,104 (16.1)
Never	54,557 (72.7)
Unknown	4412 (5.9)
Median household income, N (%)	
<$40,000	8298 (11.1)
$40,000–$79,999	41,972 (56)
>=$80,000	21,495 (28.7)
Missing	3245 (4.3)
College education, N (%)	
No	44,378 (59.2)
Yes	27,387 (36.5)
Missing	3245 (4.3)
Medicaid status, N (%)	243 (0.3)
Charlson comorbidity score, N (%)	
0	53,385 (71.2)
1	14,715 (19.6)
2+	6910 (9.2)
Diagnosis Month (2020), N (%)	
March	1846 (2.5)
April	5681 (7.6)
May	5505 (7.3)
June	18,704 (24.9)
July	31,405 (41.9)
August	11,869 (15.8)
Pollution Exposure Variables, Mean (SD)	
Non-freeway NOx (ppb)	
1 month	0.5 (0.38)
1 year	0.7 (0.51)
Freeway NOx (ppb)	
1 week	0.8 (1.14)
1 year	1.0 (1.33)
Total NOx (ppb)	
1 week	1.3 (1.25)
1 year	1.7 (1.50)
PM$_{2.5}$ (µg/m^3)	
1 week	12.7 (5.7)
1 month	11.8 (3.36)
1 year	11.0 (1.51)
4 years	11.4 (1.69)
NO$_2$ (ppb)	
1 week	8.9 (3.74)
1 month	8.7 (3.27))
1 year	13.9 (3.67)
4 years	14.6 (3.89)
O$_3$ (ppb)	
1 week	55.6 (13.94)
1 month	54.2 (11.96)
1 year	47.3 (5.64)

Table 1 (*continued*)

	Total COVID-19 Cases (N = 75,010)
4 years	47.2 (5.43)
Outcomes, N (%)	
COVID-related Hospitalization within 30 Days	4757 (6.3)
COVID-related IRS within 30 Days	1764 (2.4)
COVID-related ICU within 30 Days	1125 (1.5)
Mortality within 60 Days	1090 (1.5)

No significant effect modifications by age groups and sex were observed for the associations of non-freeway NRAP with COVID-19 severity and mortality (all interaction p > 0.05) (Supplemental Tables 5 and 6). However, the stratified analysis suggested that the associations of non-freeway NRAP with COVID-19-related mortality were non-significantly stronger among individuals 65 years or older [HRs (95% CIs) = 1.26 (1.07, 1.49) for 1-year exposure] (Supplemental Table 5). Also, associations of 1-year and 1-month non-freeway NRAP with COVID-19-related IRS, ICU admission and mortality were non-significantly larger among females than males (Supplemental Table 6). The only significant interaction was observed for 1-year non-freeway NRAP with race/ethnicity for the association with COVID-19-related IRS (interaction p = 0.02), with a larger effect size in non-Hispanic White group compared to the other race/ethnicity groups (Supplemental Table 7).

4. Discussion

In this multiethnic cohort including over 75,000 COVID-19 patients diagnosed before 08/31/2020 in Southern California, we found that non-freeway NRAP exposures were associated with a spectrum of COVID-19 severity and mortality outcomes, but not with COVID-19-related hospitalization. No significant associations were observed for freeway NRAP with COVID-19 outcomes. Regional PM$_{2.5}$ and NO$_2$ exposures did explain some of the associations between non-freeway NRAP and COVID-19 severity and mortality, but the associations remained significant after adjusting for regional air pollutant exposures. No significant interactions of age groups and sex were observed.

Air pollution exposure including traffic-related air pollution exposure has been associated with higher risk of COVID-19 incidence and mortality. (Wu et al., 2020; Bianconi et al., 2020; Andrée, 2020; Yao et al., 2020; Travaglio et al., 2021; Pozzer et al., 2020; Hutter et al., 2020; Cole et al., 2020) National data from the ecological studies has suggested that long-term exposures to PM$_{2.5}$ and NO$_2$ were associated with increased COVID-19 mortality in the United States. (Wu et al., 2020; Liang et al., 2020) Considering the known effects of air pollution on respiratory infection and chronic diseases such as cardiometabolic diseases, asthma, and chronic obstructive pulmonary disease (COPD), air pollution may also affect COVID-19 severity and mortality. (Langrish et al., 2012; An et al., 2018; Lawal, 2017; Lin et al., 2018) Since ambient NO$_2$ has been used as a tracer of traffic emission in many urban cities, traffic-related air pollution can contribute to the adverse effect of ambient air pollution on COVID-19 severity. Like PM$_{2.5}$ and NO$_2$, traffic-related air pollution has been shown to increase systemic inflammation, which may play a role in the mechanism of severe COVID-19. (Lanki et al., 2015; Rich et al., 2012) Based on this hypothesis, an ecological study investigated the association of historical NO$_2$ exposure in 2016, as a representative of traffic-related air pollution estimated by the land-use regression model, with COVID-19 incidence and mortality in the Los Angeles area from 03/16/2020 to 02/23/2021. (Lipsitt et al., 2021) Researchers found that an interquartile range (8.7 ppb) increase in historical NO$_2$ exposure was associated with a 27% and 34% increased incidence and case fatality rate, respectively, in Los Angeles County. However, to our knowledge, no cohort studies with individual-level NRAP exposure and outcome and comorbidity adjustment have been
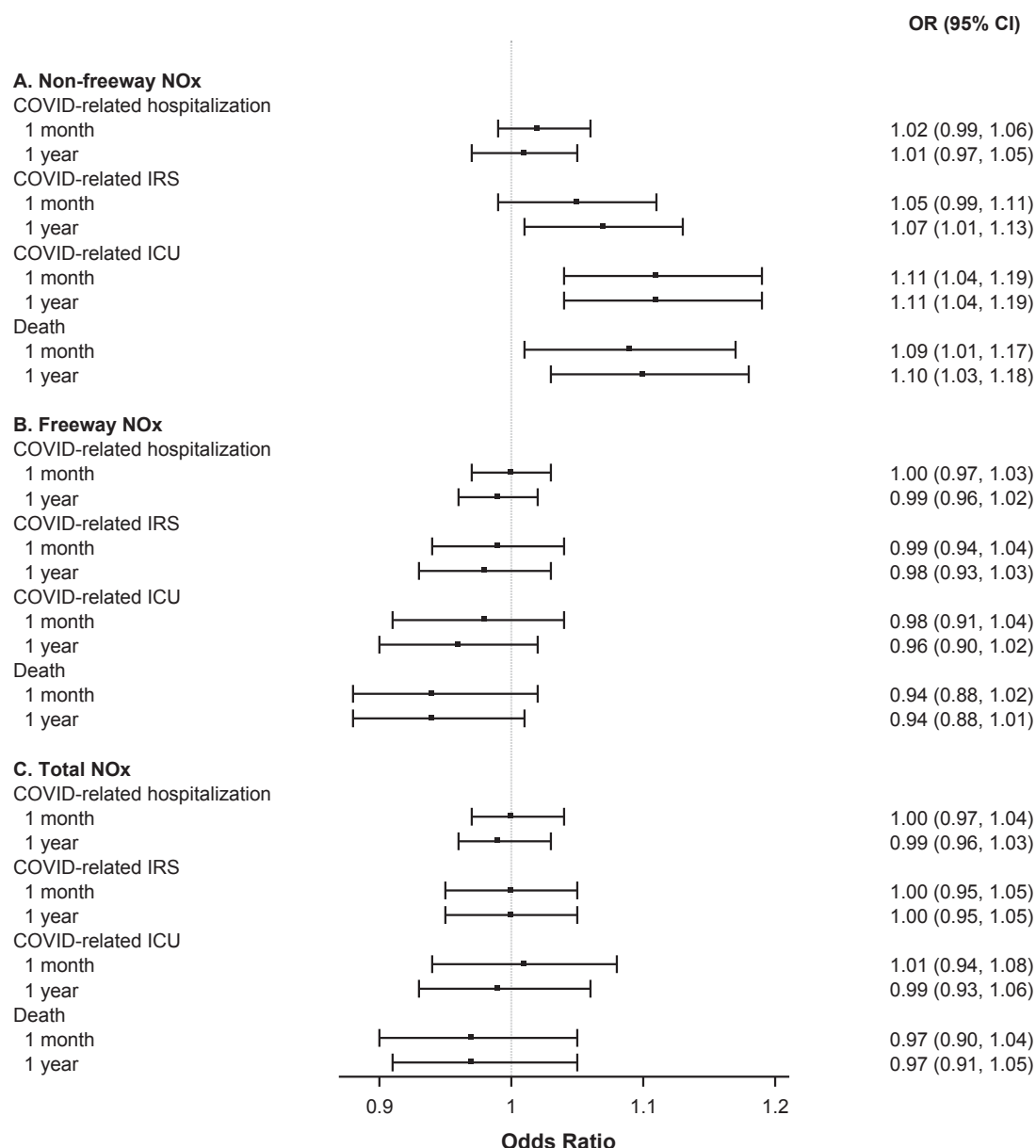
Fig. 1. Associations between near-roadway air pollution (NRAP) exposures including (a) non-freeway NOx, (b) freeway NOx, and (c) total NOx with COVID-19 severity and mortality. Measure of association is hazard ratio for death. All models adjusted for age group, gender, race/ethnicity, income, college education, Medicaid insurance status, BMI category, smoking and modified Charlson comorbidity score.

conducted to robustly examine these associations -a gap our study aims to fill.

Findings from our study with individual-level data consistently show that NRAP exposure is a risk factor of COVID-19 severity. Furthermore, our results indicate that the effects from freeway and non-freeway sources may be different. In this study, non-freeway NRAP exposures were particularly associated with higher risk of a spectrum of COVID-19 severity outcomes including IRS, ICU admission and mortality, while there were no significant associations for freeway NRAP. Different associations with non-freeway or freeway air pollution exposures have also been observed for other respiratory and cardiometabolic outcomes that are known as comorbidities for severe COVID-19. (Kim et al., 2018; Eckel et al., 2011; Chen et al., 2019; McConnell et al., 2015) In a children's cohort study in Southern California, researchers found that the total length of local roads near residences were associated with increased exhaled nitric oxide, which suggested that chronic traffic exposure from local roads could increase airway inflammation. (Eckel

et al., 2011) Chronic exposure to non-freeway NRAP has also been observed to increase the risk of childhood obesity and altered lipid metabolism in young adults. (Kim et al., 2018; Chen et al., 2019; McConnell et al., 2015) Our results suggest that high level of non-freeway NRAP exposure may increase the risk of having a severe outcome after COVID-19 infection and the effect seems beyond the adverse effects on respiratory and cardiometabolic systems since these comorbidities were already adjusted for in our models. We speculate that the different associations between freeway and non-freeway NRAP might be attributed to the fact that the chemical composition of NRAP exposure from freeway versus non-freeway roads can vary across vehicle types and vehicle volume. (Fujita et al., 2007) Freeway NRAP is largely comprised of diesel and gasoline combustion products, which decay exponentially by the distance to freeways. (Gilbert et al., 2005; Zhu et al., 2002) In contrast, non-freeway NRAP exposure contains more non-exhaust particles (e.g., brake wear and tire wear). Of note, Southern California, where the study cohort was drawn, has less density in
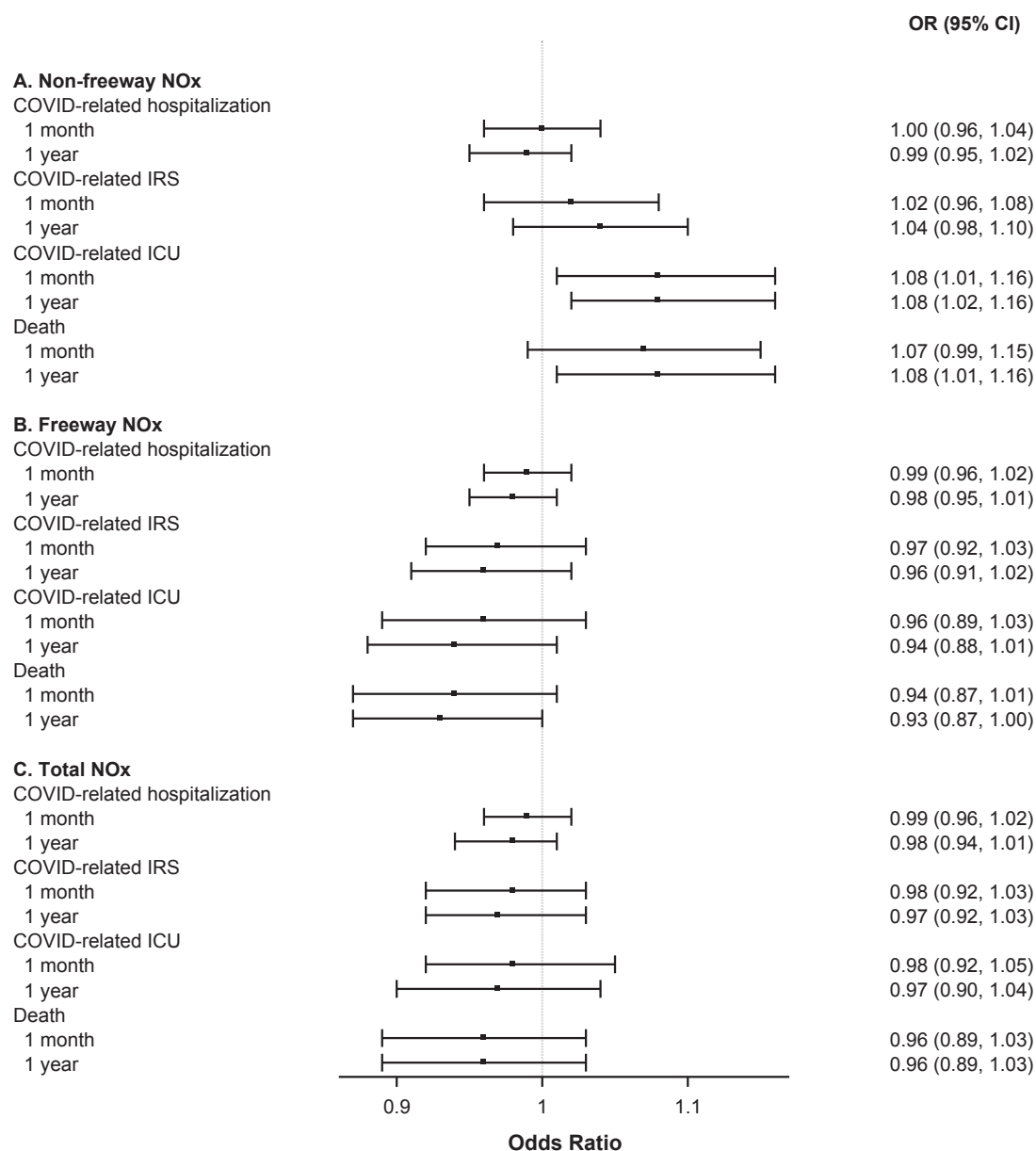
OR (95% CI)

A. Non-freeway NOx
COVID-related hospitalization
   1 month   1.00 (0.96, 1.04)
   1 year   0.99 (0.95, 1.02)
COVID-related IRS
   1 month   1.02 (0.96, 1.08)
   1 year   1.04 (0.98, 1.10)
COVID-related ICU
   1 month   1.08 (1.01, 1.16)
   1 year   1.08 (1.02, 1.16)
Death
   1 month   1.07 (0.99, 1.15)
   1 year   1.08 (1.01, 1.16)

B. Freeway NOx
COVID-related hospitalization
   1 month   0.99 (0.96, 1.02)
   1 year   0.98 (0.95, 1.01)
COVID-related IRS
   1 month   0.97 (0.92, 1.03)
   1 year   0.96 (0.91, 1.02)
COVID-related ICU
   1 month   0.96 (0.89, 1.03)
   1 year   0.94 (0.88, 1.01)
Death
   1 month   0.94 (0.87, 1.01)
   1 year   0.93 (0.87, 1.00)

C. Total NOx
COVID-related hospitalization
   1 month   0.99 (0.96, 1.02)
   1 year   0.98 (0.94, 1.01)
COVID-related IRS
   1 month   0.98 (0.92, 1.03)
   1 year   0.97 (0.92, 1.03)
COVID-related ICU
   1 month   0.98 (0.92, 1.05)
   1 year   0.97 (0.90, 1.04)
Death
   1 month   0.96 (0.89, 1.03)
   1 year   0.96 (0.89, 1.03)

0.9   1   1.1

Odds Ratio

Fig. 2. Associations between near-roadway air pollution (NRAP) exposures including (a) non-freeway NOx, (b) freeway NOx, and (c) total NOx with COVID-19 severity and mortality, further adjusting for regional air pollutants exposures of PM$_{2.5}$ and NO$_2$. Measure of association is hazard ratio for death. All models adjusted for age group, gender, race/ethnicity, income, college education, Medicaid insurance status, BMI category, smoking, modified Charlson comorbidity score, PM$_{2.5}$ and NO$_2$.

freeways and thus fewer residents live near freeways compared to some other major metropolitan cities. Taken together, these results support a need of future studies to identify specific components or chemicals of NRAP that are detrimental to health outcomes.

Strengths of this study include individual-level NRAP exposures, multiple COVID-19-related outcomes, and comprehensive covariate data collected from a large multiethnic cohort of COVID-19 patients with confirmed diagnosis in the KPSC EMR. The KPSC members cover 20% of the entire population in Southern California and the socio-demographic characteristics are comparable to the general population in Southern California. (Koebnick et al., 2012) Uniform guidelines were used across all KPSC medical centers throughout the pandemic period, which guaranteed that all KPSC members have equal access to COVID-19 testing and treatment options. The unique study population built upon the KPSC membership system helps to minimize the potential influence of testing, case ascertainment, and hospital capacity that varied

over the time. We also included months of diagnosis as a fixed covariate in our analysis to further minimize the residual bias due to the unknown dynamic confounders. Secondly, the cutting-edge CALINE4 exposure model was used to obtain estimates of daily NRAP level across the residential history during one year before the COVID-19 diagnosis, so we were able to investigate the NRAP exposure effect in various time windows from 1-month to 1-year periods. The exposure data also helped identify separate roles of freeway and non-freeway NRAP in COVID19-severity. Lastly, we adjusted for detailed socio-characteristics and co-morbidity history in the analysis and tested for potential effect modifications across subgroups of age, sex, and race/ethnicity.

We acknowledge several limitations of our study. First, only COVID-19 cases diagnosed during the earlier pandemic period before 08/31/2020 were included in this study. Lower testing accessibility and sensitivity during the early pandemic might influence the case ascertainment in this study. However, the study cohort included all COVID-19

cases for all KPSC members aged ≥ 12 years. KPSC uses uniform diagnosis and management guidelines for all members across all medical centers. The outcomes included in this study were COVID-19 related hospitalization, ICU admission, intensive respiratory support, and death after COVID-19 diagnosis, all of which were extracted from the EMR for each individual case. Thus, we expect no to minimal ascertainment bias for the outcomes. Our finding was consistent with the previous ecological analysis of traffic-related air pollution in association with COVID-19 incidence and mortality in Los Angeles. That study found comparable findings from the later period of 09/08/2020 to 02/23/2021. We will continue to follow our recent EMR data in future studies to validate our findings in COVID-19 cases identified after 08/31/2020. Since several more transmissible SARS-CoV-2 variants have been found after our study period (*https://nextstrain.org/ncov/gisaid/global*), future studies are needed to compare the NRAP effect across various SARS-CoV-2 variants and across earlier *vs.* later pandemic periods. Second, although both longer- and shorter-term NRAP were investigated in this study, we could not clearly distinguish the shorter-term from the longer-term exposure effects due to the high temporal correlations (R > 0.9). We generally observed that 1-month and 1-year non-freeway NRAP were both consistently associated with COVID-19 related IRS, ICU admission and mortality, with the effect size of the 1-month exposure slightly smaller than that of the 1-year exposure. We also assessed the independent effect of NRAP from ambient air pollution exposure. Although adjusting for ambient $PM_{2.5}$ and NO_2 attenuated the effect size of non-freeway NRAP, the associations between non-freeway NRAP and COVID-19-related ICU admission and mortality remained significant. Third, we did not assess indoor exposures, the built environment, and occupation-related exposures, which would require time activity and personal monitoring data. Future studies are needed to investigate both indoor and outdoor air pollution effects on COVID-19 outcomes. Individual and family occupations, household crowding, as well as adherence to public interventions such as wearing masks and social distancing are important factors contributing to infection, but they are hard to capture at the individual level in large population studies. Future studies incorporating mobile data collection tools to dynamically obtain individual-level data could help to enhance this component of COVID-19 research. Lastly, although the diverse sociodemographic characteristics of KPSC members are comparable to the residents of Southern California (Koebnick et al., 2012) and all individuals included in this study had commercial, private, Medicare or Medicaid insurance, the findings of this study may not be generalizable to some specific populations. Although we assessed multiplicative interactions with age, sex and race/ethnicity and no statistically significant multiplicative interactions were observed, testing for additive interactions could enhance public health interpretations. Since testing additive interactions would require all categorical variables, future studies may pursue this by categorizing NRAP exposure into levels based on known public health risk.

In conclusion, data from this large multiethnic cohort of COVID-19 infected patients in Southern California suggest that traffic-related air pollution exposure, particularly air pollution from non-freeway traffic, may be associated with elevated risk of COVID-19 severity and mortality. The risk appears consistent across different age, sex, and race/ethnicity groups. Future studies are needed to assess the impact of emerging COVID-19 variants and chemical component differences between freeway and non-freeway NARP and their impact on health outcomes.

5. Data statement

KPSC Institutional Review Board approved this study, with waiver of informed consent with the condition that raw data remains confidential and would not be shared. Thus, due to the sensitive nature of this data, the data is not available to be shared.

Author contributions

Z.C., M.A.S., B.Z.H., F.D.G., and A.H.X. were responsible for the study concept and design. A.H.X. and Z.C. obtained funding. A.H.X., Z. C., M.A.S., B.Z.H., T.C., S.P.E., M.P.M., R.G., F.L., N.P., D.C.T., and F.D. G. conducted the study. B.Z.H., M.A.S., T.C., M.P.M., and A.H.X., acquired data. B.Z.H, M.A.S., T.C., and A.H.X. analyzed data. Z.C., M.A.S., B.Z.H, R.G., and A.H.X. drafted the manuscript. All authors revised the manuscript for important intellectual content and approved the final version to be published.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106862.

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